Sector 1775

PATENT

Attorney Docket No.: A-68990-3/RFT/RMS/RMK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

DAHIYAT et al.

Serial No. 09/981,289

Filed: October 15, 2001

For: DESIGN AND DISCOVERY OF PROTEIN BASED TNF-α VARIANTS FOR THE TREATMENT OF TNF-α RELATED DISORDERS

Examiner: Unknown

Group Art Unit: 1645

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Commissioner of Patents and Trademarks, BOX INITIAL PATENT EXAMINATION DIVISION, MISSING PARTS/FEE, Washington, DC 20231 on January 7, 2002.

Signed: Mary McFarland

Mary McFarland

Assistant Commissioner of Patents
Washington, DC 20231
BOX: INITIAL PATENT EXAMINATION DIVISION
MISSING PARTS/FEE

PRELIMINARY AMENDMENT RE: SEQUENCE LISTING

Sir:

This is in response to the Notice to File Missing Parts of Nonprovisional Application dated November 5, 2001.

The present Preliminary Amendment is submitted to comply with requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosures. The Commissioner is authorized to charge any additional fees including extension fees or other relief which may be required, or credit any overpayment to Deposit Account No. 06-1300 (Our Order No. A-68990-3/RFT/RMS/RMK).

Please amend the specification in adherence with rules 37 C.F.R. § 1.821-1.825 as follows:

IN THE SPECIFICATION:

Please replace the paragraph beginning at page 3, line 18, with the following rewritten paragraph:

– Figure 6A (SEQ ID NO:1) depicts the nucleotide sequence of the histidine tagged wild-type TNF-α molecule used as a template molecule from which the mutants were generated. The additional 6 histidines, located between the start codon and the first amino acid are underlined.–

Please replace the paragraph beginning at page 3, line 21, with the following rewritten paragraph:

– Figure 6B (SEQ ID NO:2) depicts the amino acid sequence of wild-type TNF-α with an additional 6 histidines (underlined) between the start codon and the first amino acid. Amino acids changed in the TNF-α mutants are shown in bold. –

Please replace the paragraph beginning at page 4, line 13, with the following rewritten paragraph:

– Figure 12 (SEQ ID NOS:3-8) depicts trimerization domains from TRAF proteins. –

Please replace the paragraph beginning at page 21, line 26, with the following rewritten paragraph:

– The TNF-α proteins may be from any number of organisms, with TNF-α proteins from mammals being particularly preferred. Suitable mammals include, but are not limited to, rodents (rats, mice, hamsters, guinea pigs, etc.), primates, farm animals (including sheep, goats, pigs, cows, horses, etc); and in the most preferred embodiment, from humans (the sequence of which is depicted in Figure 6; SEQ ID NO:2). As will be appreciated by those in the art, TNF-α proteins based on TNF-α proteins from mammals other than humans may find use in animal models of human disease. –

Please replace the paragraph beginning at page 25, line 16, with the following rewritten paragraph:

– The variant TNF-α proteins and nucleic acids of the invention are distinguishable from naturally occurring wild-type TNF-α. By "naturally occurring" or "wild type" or grammatical equivalents, herein is meant an amino acid sequence or a nucleotide sequence that is found in nature and includes allelic variations; that is, an amino acid sequence or a nucleotide sequence that usually has not been intentionally modified. Accordingly, by "non-naturally occurring" or "synthetic" or "recombinant" or grammatical equivalents thereof, herein is meant an amino acid sequence or a nucleotide sequence that is not found in nature; that is, an amino acid sequence or a nucleotide sequence that usually has been intentionally modified. It is understood that once a recombinant nucleic acid is made and reintroduced into a host cell or organism, it will replicate non-recombinantly, i.e., using the in vivo cellular machinery of the host cell rather than in vitro manipulations, however, such nucleic acids, once produced recombinantly, although subsequently replicated non-recombinantly, are still considered recombinant for the purpose of the invention. Representative amino acid and nucleotide sequences of a naturally occurring human TNF-α are shown in Figure 6 (SEQ ID NOS:1-2). It should be noted that unless otherwise stated, all positional numbering of variant TNF-α proteins and variant TNF-α nucleic acids is based on these sequences. That is, as will be appreciated by those in the art, an alignment of TNF-α proteins and variant TNF-α proteins can be done using standard programs, as is outlined below, with the identification of "equivalent" positions between the two proteins. Thus, the variant TNF-α proteins and nucleic acids of the invention are non-naturally occurring; that is, they do not exist in nature.

Please replace the paragraph beginning at page 28, line 4, with the following rewritten paragraph:

– Thus, the variant TNF-α proteins of the present invention may be shorter or longer than the amino acid sequence shown in Figure 6B (SEQ ID NO:2). Thus, in a preferred embodiment, included within

the definition of variant TNF proteins are portions or fragments of the sequences depicted herein. Fragments of variant TNF-α proteins are considered variant TNF-α proteins if a) they share at least one antigenic epitope; b) have at least the indicated homology; c) and preferably have variant TNF-α biological activity as defined herein.–

Please replace the paragraph beginning at page 29, line 26, with the following rewritten paragraph:

– In one embodiment, the nucleic acid homology is determined through hybridization studies. Thus, for example, nucleic acids which hybridize under high stringency to the nucleic acid sequence shown in Figure 6A (SEQ ID NO:1) or its complement and encode a variant TNF-α protein is considered a variant TNF-α gene.–

On page 61 , immediately preceding the claims, please insert the enclosed text entitled "SEQUENCE LISTING".

REMARKS

Entry of this amendment is respectfully requested. The amendments are made in adherence with 37 C.F.R. § 1.821-1.825. This amendment is accompanied by a floppy disk containing the above named sequence, SEQUENCE ID NUMBERS 1-8, in computer readable form (CRF), and a paper copy of the sequence information. The computer readable sequence listing was prepared through use of the software program "PatentIn" provided by the PTO. The information contained in the computer readable disk is identical to that of the paper copy. This amendment contains no new matter. Applicant submits that this amendment, the accompanying computer readable sequence listing, and

the paper copy thereof serve to place this application in a condition of adherence to the rules 37 C.F.R. § 1.821-1.825.

Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP

Dated: _______________ ______________________________

Four Embarcadero Center
Suite 3400
San Francisco, CA 94111-4187
Telephone: (415) 781-1989

Robin M. Silva, Reg. No. 38,304

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Paragraph beginning at page 3, line 18, has been amended as follows:

– Figure 6A (SEQ ID NO:1) depicts the nucleotide sequence of the histidine tagged wild-type TNF-α molecule used as a template molecule ~~form~~ from which the mutants were generated. The additional 6 histidines, located between the start codon and the first amino acid are underlined.–

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Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP

Dated: 1/7/02

Robin M. Silva, Reg. No. 38,304

Four Embarcadero Center
Suite 3400
San Francisco, CA 94111-4187
Telephone: (415) 781-1989